REMARKS

The Office Action dated April 2, 2010 has been received and carefully reviewed. The following remarks form a full and complete response thereto. No new matter has been added. Claims 30-38, 42-43, and 46-57 are pending in the application and are submitted for reconsideration.

Rejection under 35 U.S.C. § 103

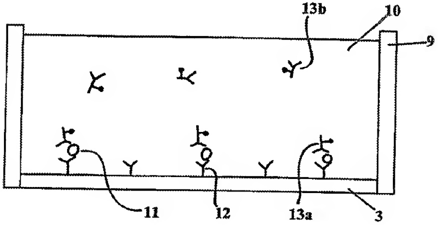
The Office Action has rejected claims 30-34, 37, 38, 42, 43, 46-53, 56 and 57 under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,622,868 to Clarke et al. (Clark), in view of U.S. Patent No. 7,244,572 to Schwabacher and U.S. Patent Publication No. 2003/0005771 to Percin et al. (Percin). Applicants now traverse this rejection in full.

Claim 30 is directed to a device for detecting energy generated by non-radiative decay in an analyte or a complex or derivative of the analyte on irradiation with electromagnetic radiation. The device includes a radiation source adapted to generate a series of pulses of electromagnetic radiation. The device further includes a transducer having a pyroelectric or piezoelectric element and electrodes which is capable of transducing the energy generated by the substance into an electrical signal. The device further includes at least one reagent proximal to the transducer. The reagent having a binding site which is capable of binding the analyte or the complex or derivative of the analyte. The device further includes a well for holding a liquid having the analyte dissolved or suspended therein in context with the transducer.detector which is capable of detecting the electrical signal generated by the transducer. The detector is adapted to determine the time delay between each pulse of electromagnetic radiation from the radiation source and the generation of the electric signal, wherein the time delay is no greater than 150 milliseconds.

Claim 49 is directed to a method for detecting an analyte dissolved or suspended in a liquid sample. The method includes a step of exposing the liquid sample containing the dissolved or suspended analyte, to a transducer having a pyroelectric or piezoelectric element and electrodes which is capable of transducing a change in energy to an electrical signal. The transducer having at least one reagent proximal to the transducer. The reagent has a binding site

which is capable of binding the analyte or a complex or derivative of the analyte. The analyte, complex, or derivative of the analyte being capable of absorbing the electromagnetic radiation generated by the radiation source in order to generate energy by non-radiative decay. The method includes a step of irradiating the reagent with a series of pulses of electromagnetic radiation. The method includes a step of transducing the energy generated into an electrical signal. The method includes a step of detecting the electrical signal and the time delay between each pulse of electromagnetic radiation from the radiation source and the generation of the electric signal, wherein the time delay between each of the pulses of electromagnetic radiation and the generation of the electric signal is no greater than 150 milliseconds and corresponds to the position of the analyte at any of one or more positions at different distances from the surface of the transducer.

The current invention is an improvement over the prior art in the field for at least the reason that it allows a user to detect a bound analyte in the presence of a bulk solution or of a suspension containing unbound analyte. That is, in a liquid sample, an analyte bound near to the surface of a transducer can be distinguished from an analyte dissolved or suspended in the liquid sample. This can be explained in view of Fig. 2 of the present application, as shown below.



In conducting an assay using the present invention, the whole sample is irradiated and both the bound analyte (13a) and the unbound analyte (13b) will generate a signal. The signal from the unbound analyte will reach the transducer (3), but it will not be detected because of the cut-off in the time delay. This ability to distinguish between the bound and unbound analytes is described throughout the specification and is accomplished, at least in part, by "depth profiling."

See pg. 5, lns. 24-25 of the current application. Utilizing the current invention, a number of binding assays, such as immunoassays (e.g., ELISA), to be carried out without waiting for each assay to finish and then washing away the remaining unbound analyte. This is a significant improvement over the prior art which require a washing step, as described below.

Additionally, Applicants note that the ability to conduct "depth profiling" using the "time delay," as recited in claims 30 and 49, is a wholly unexpected result. Indeed, Applicant's expected the liquid in which the analytes are dissolved or suspended to interfere with or dissipate the heat generated by the irradiated substance. However, this surprisingly is not the case. This unexpected result buttresses the non-obvious nature of the present invention. See MPEP § 2141.

In contrast, Clarke is generally directed to an analytical apparatus utilizing a colormetric or other optically detectable effect. More particularly, Clarke discloses an apparatus for detecting optical effects on the surface of a transducer. See Clarke col. 2, lns. 16-26, 34-36; col. 3, lns. 1-9; col. 4, lns. 25-27. This is the type of prior art already disclosed in and discussed by the current specification at pg. 1, lns. 13-33. Additionally, Applicants note that the Office Action admits that Clarke does not disclose "that the processor is adapted to measure the delay from the time a pulse of radiation from the light source is generated and a signal from the reagent is detected" or "wells for holding liquids." See Office Action pg. 3, para. 2. Because Clarke does not disclose a processor adapted to measure the delay from the time a pulse of radiation from the light source is generated and a signal from the reagent is detected, bound analytes cannot be distinguished from unbound analytes. Thus, when performing an immunoassay, such as ELISA (see Clarke col. 4, lns. 49-53), Clarke requires a washing step to ensure that the unbound analytes do not provide false positives.

The teachings of Schwabacher pertain to optical fibers which "provide[] a unique substrate of which chemosensors, combinatorial libraries, or other agents can be linearly arrayed and can be assayed based on a change in optical property." See Schwabacher col. 6, lns. 11-14 (emphasis added). More particularly, Schwabacher discloses the use of linear arrays of chemosensors, supported by an optical fiber, which can be used to rapidly assay the entire array using changes in the optical properties along the optical fiber. See Schwabacher Abstract. Additionally, Schwabacher discloses that "[t]he individual agents can be identified by their location along the fiber, and the time delay between delivering light and detecting a change in light can be used to determine the location and therefore the identity of the compound." See

Schwabacher col. 6, lns. 14-18.

Percin is generally directed to a two-dimensional array of ultrasonic sensors for high throughput fluid screening. The Office Action cites Percin as disclosing "a well for holding a liquid having the analyte dissolved or suspended therein in contact with the transducer," as recited in claim 30.

Applicants contend that the cited references, considered alone or in combination, fail to teach or suggest the claimed invention. For example, Clarke fails to disclose: "a detector which is capable of detecting the electrical signal generated by the transducer, wherein the detector is adapted to determine the time delay between each pulse of electromagnetic radiation from the radiation source and the generation of the electric signal, and wherein the time delay is no greater than 150 milliseconds," as is recited in claim 30 (and similarly recited in claim 49). As discussed above, one feature of the present invention is that of depth profiling, namely the ability to distinguish between a bound and unbound analyte in proximity to the transducer. Depth profiling is accomplished, in part, by finding a time delay between each pulse of electromagnetic radiation from the radiation source and the generation of the electric signal. In order to measure this precise time delay the detector must be configured to take readings up to a time delay of 150 milliseconds. As noted above, Clarke fails to disclose that the processor is adapted to measure the delay from the time a pulse of radiation from the light source is generated and a signal from the reagent is detected. Thus, Clarke fails to disclose that the measured time delay is no greater than 150 milliseconds, as is recited in both pending independent claims.

Schwabacher fails to cure the defects of Clarke. Schwabacher fails to disclose that the measured time delay is no greater than 150 milliseconds, as is recited in both claims 30 and 49. Schwabacher discloses finding the location of individual agents along the fiber in order to identify the compound. <u>See</u> Schwabacher col. 6, lns. 14-18. Thus, the detector of Schwabacher will measure all time delays in order to correlate them to the compound locations on the optical fiber. This is different from the current invention, which claims the measured time delay to <u>no greater</u> than 150 milliseconds in order to differentiate the bound and the unbound analytes in a solution or sample.

Additionally, Figure 8 of Schwabacher describes the embodiment in that document in which the whole sample is irradiated. The light is absorbed by the chromophore (in Figure, 8 it is a fluorophore) and the light emitted from the excited chromophore is then absorbed by the relevant part of the optical fiber and that absorption is detected by the detector. However, this approach could only determine the presence or absence of <u>any</u> given chromophore in the sample <u>as a whole</u>, it could not <u>distinguish</u> between bound and unbound versions of the same chromophore as they would both be absorbed at essentially the same time <u>by the same reactant region</u> in the optical fiber. Other regions on the optical fiber would not provide any further information. This is because each individual region on the optical fiber contains a different reagent. <u>See</u> Schwabacher col. 2, ln. 66 – col. 3, ln. 5 and col. 6, lns. 14-18. If that reagent were a label on an analyte (as in Clarke), the signal received by the reagent on the optical fiber from <u>bound and unbound</u> label would be the same and so no distinction could be made. For this reason, the combination of Clarke, Schwabacher, and Percin would not yield a detector adapted to determine the time delay between pulses because, according to the combination, there would be substantially <u>no time delay</u> to determine.

For at least the above described reasons, the cited prior art fails to teach, suggest, or disclose each and every limitation of claims 30 and 49. Thus, claims 30 and 49 are currently allowable. Because independent claims 30 and 49 are patentable, defendant claims 31-34, 37-38, 42-43, 46-48, 50-53, and 56-57 are likewise patentable. Applicants respectfully request that the current rejection be withdrawn.

Additionally, one of ordinary skill in the art would only combine the teachings of Clarke, Schwabacher, and Percin using <u>impermissible hindsight</u>. Applicants note that the scales involved in the present invention are <u>very small</u>. Although Fig. 2 of the present application, shown above, shows a large distance between bound and unbound analyte, in reality, the unbound analyte is free to diffuse throughout the whole sample. Thus, potentially interfering unbound analyte will be close to the bound material. One of ordinary skill in the art would recognize that this closeness is inherent to the technique given that the transducer is immersed in the liquid sample containing the analyte. Clarke is likewise designed to operate on this small scale.

By contrast, the scale at which Schwabacher is meant to operate is gargantuan. The optical fiber in Schwabacher has spacing between reactant regions on the centimeter scale. See Schwabacher col. 11, lns. 5-8 (which discloses a minimum spacing between reactant regions (d_{min}) of 10 cm.). This wide spacing in Schwabacher is essential because the optical fiber and detection apparatus uses the time taken for light to propagate through the fiber to provide information on the different positions along the fiber providing a signal. Id. The speed of light provides limitations on the spacing because of the minute differences in time which must be detected in the system of Schwabacher. See Schwabacher col. 13, lns. 28-31. Thus, the technology of Schwabacher is only applicable to systems that detect large differences in distance (e.g., of the order of centimeters).

Contrary to the Office Action's assertion that Schwabacher "is applicable to all similar analytical devices that utilize a light source to irradiate a sample and detect a signal induced by radiation," the above described scale discrepancy obviates Schwabacher's applicability to the current invention. One of ordinary skill in the art would immediately recognize that the teaching of Schwabacher are wholly inapplicable to the present invention which requires measurements over a scale of microns or even nanometers (because the unbound analyte can diffuse so closely to the bound analyte) rather than the centimeters described in Schwabacher. Thus, one of ordinary skill in the art would find no reason, other than impermissible hindsight, to combine the teachings of Clarke, Schwabacher, and Percin.

Further, Schwabacher specifically notes that optical fibers "provide[] a unique substrate of which chemosensors, combinatorial libraries, or other agents can be linearly arrayed and can be assayed based on a change in optical property." See Schwabacher col. 6, lns. 11-14 (emphasis added). That is, optical fibers are unlike other known substrates for performing assays. Thus, one of ordinary skill in the art would apply the teachings of Schwabacher only to other optical fiber systems knowing full well that optical fiber systems utilize a "unique substrate." Thus, one of ordinary skill in the art would find no reason, other than impermissible hindsight, to combine the teachings of Clarke, Schwabacher, and Percin.

Moreover, the Office Action's combination of Schwabacher and Clarke is impermissible hindsight reasoning. That is, assuming *arguendo* that one of ordinary skill in the art would apply the teachings of Schwabacher to a non-optical fiber system, one of ordinary skill in the art would not venture so far as to apply Schwabacher to a completely divergent technical approach. That is, the system described in Schwabacher is concerned with the measurement of photons. In contrast, the Clarke, like the present invention, utilizes a pyroelectric/piezoelectric transducer which measures the generation of heat and shock waves from a sample. These are two divergent technical approaches and one skilled in the art would not look to one when seeking to improve the other. One of ordinary skill in the art certainly would have no expectation that he could successfully apply principles from the detection of photons to the detection of a heat signals by a pyroelectric/piezoelectric transducer. Moreover, there would be no expectation of being able to provide a technically meaningful signal from such an experiment. Consequently, one of ordinary skill in the art would not combine Clarke and Schwabacher in order to solve the problem of the present invention, i.e. being the ability to distinguish between bound and unbound analyte utilizing depth profiling in a pyroelectric/piezoelectric transducer system.

Additionally, the Office Action's combination of Clarke and Percin is impermissible hindsight reasoning. As described above, Clarke is a system that requires a washing step in order to remove unbound analytes from the assay. If the system of Clarke had wells, this washing step would be prone to error because liquid containing unbound analyte would be prevented from washing away. Wells, by their very nature, serve to maintain liquid in a particular location by providing physical boundaries in which liquid is contained. These boundaries would hinder the washing step formed in an assay, such as ELISA. The current invention can perform an assay <u>without washing</u>, and thus can use wells without degrading the results of an assay.

Finally, Applicants note that they were able to use the signal time delay as a means for measurement because <u>they discovered</u> that the signal propagates through the liquid medium by means of thermal diffusion (<u>i.e.</u>, non-radiative decay). Thus, the independent claims of the present application are directed to a "device for detecting energy generated by non-radiative decay in a substance on irradiation with electromagnetic radiation" and the transducer has a "pyroelectric or piezoelectric element" which detects such decay. Thus, although the initial signal is generated by irradiating the sample with light, the label interacts with the light to

generate heat which produces the thermal diffusion. The heat propagates much more slowly through the medium than light, allowing the detector to distinguish different positions. <u>This was not apparent to the skilled person starting from Clarke without having the benefit of hindsight in view of the present application</u>. The Office Action over simplifies the invention and fails to distinguishe between different types of induced signal (non-radiative vs. radiative decay, <u>i.e.</u>, thermal diffusion vs. light).

Thus, the combination Clarke, Schwabacher, and Percin suggested by the Office Action is purely impermissible hindsight. Claims 30-34, 37, 38, 42, 43, 46-53, 56 and 57 are allowable over the impermissible combination of Clarke, Schwabacher, and Percin for these additional reasons. Applicants respectfully request that this rejection be withdrawn.

The Office Action has rejected claims 35, 36, 54 and 55 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Clarke in view of Schwabacher and Percin, and further in view of U.S. Patent No. 6,306,598 to Charych et al. (Charych). The Office Action cites to Charych et al. as allegedly disclosing the use of avidin/biotin conjugate to bind an analyte of interest. However, because Charych fails to cure the deficiencies described in detail above, claims 35, 36, 54 and 55 are patentable over the prior art. Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the above, all objections and rejections have been overcome. The Applicants submit that the application is now in condition for allowance and request that claims 30-38, 42-43, and 46-57 be allowed and this application passed to issue.

In the event that this paper is not timely filed, the Applicants respectfully petition for an appropriate extension of time. Any fees for such an extension together with any additional fees may be charged to Counsel's Deposit Account No. 02-2135.

If for any reason the Examiner determines that the application is not now in condition for allowance, it is respectfully requested that the Examiner contact, by telephone, the Applicants' undersigned attorney at the indicated telephone number to arrange for an interview to expedite the disposition of this application.

Respectfully submitted,

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